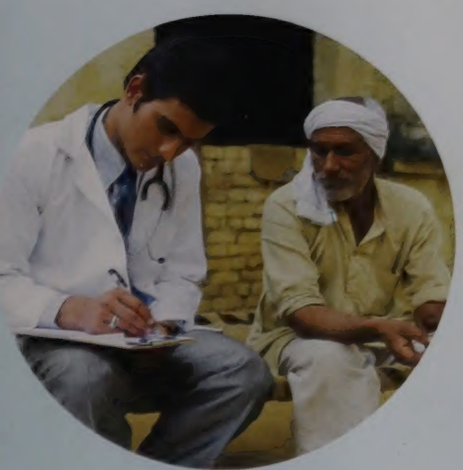
medicines
patent
pool

Challenges for the Uptake of Fixed-Dose Combinations: An Analysis of Intellectual Property Issues



Working Paper July 2012

1445
CLIC-
CPHE

SOCHARA
Community Health
Library and Information Centre (CLIC)
Centre for Public Health and Equity
No. 27, 1st Floor, 6th Cross, 1st Main
1st Block, Koramangala, Bengaluru 34
Tel : 080 - 41280009
email clic@sochara.org / cphe@sochara.org
www.sochara.org

Working paper prepared by:
Esteban Burrone, Chan Park, Suerie Moon, Natasha Sunderji, Pascale Boulet and Ellen 't Hoen.

SOCHARA
Community Health Library and Information Centre (CLIC)
Centre for Public Health and Equity
No. 27, 1st Floor, 6th Cross, 1st Main, 1st Block, Koramangala, Bengaluru-34.

THIS BOOK MUST BE RETURNED BY
THE DATE LAST STAMPED

Acronyms and Definitions

Acronyms	
AIDS	Acquired Immune Deficiency Syndrome
ARIPO	African Regional Intellectual Property Organization
ART	Antiretroviral treatment
ARV	Antiretroviral drug
BMS	Bristol Meyers Squibb
EAPO	Eurasian Patent Organization
FDA	United States Food and Drug Administration
FDC	Fixed Dose Combination
GPRM	Global Price Reporting Mechanism
HIV	Human Immunodeficiency Virus
IP	Intellectual Property
LDC	Least Developed Countries
LIC	Low Income Countries
MDC	Market Dynamics and Commodities
MSD	Merck Sharp & Dohme
MSF	Médecins Sans Frontières
OAPI	Organisation Africaine de la Proprieté Intellectuelle/African Organization of Industrial Property
SSA	Sub-Saharan Africa
TAC	Treatment Action Campaign
TRIPS	WTO Agreement on Trade-Related Aspects of Intellectual Property Rights
WHO	World Health Organization
WIPO	World Intellectual Property Organization
WTO	World Trade Organization

Antiretroviral Medicines	
3TC	Lamivudine
ABC	Abacavir
ATV	Atazanavir
AZT	Zidovudine
COB	Cobicistat
DLG	Dolutegravir
DRV	Darunavir
EFV	Efavirenz
ETV	Etravirine
EVG	Elvitegravir
FTC	Emtricitabine

Community Health Library and Information Centre
CPHE - SOCHARA
Koramangala
Bangalore - 34
DR-300
14.4.03 P12

LPV	Lopinavir
NVP	Nevirapine
RAL	Raltegravir
RIL	Rilpivirine
RTV, r	Ritonavir
TDF	Tenofovir Disoproxil Fumarate

Country Codes	
AL	Algeria
AR	Argentina
AM	Armenia
BR	Brazil
CL	Chile
CN	China
CO	Colombia
DO	Dominican Republic
EG	Egypt
GE	Georgia
GT	Guatemala
IN	India
ID	Indonesia
KG	Kyrgyzstan
MY	Malaysia
MX	Mexico
MA	Morocco
PA	Panama
PE	Peru
PH	Philippines
RU	Russian Federation
ZA	South Africa
TJ	Tajikistan
UA	Ukraine
UY	Uruguay
UZ	Uzbekistan
VN	Vietnam

Table of Contents

1 Executive Summary 1

2 Introduction and Scope of the Paper 2

3 Fixed Dose Combinations, ARVs and Patents 2

3.1 Benefits of FDCs in antiretroviral treatment 2

3.2 Impact of patents on accessibility of ARV FDCs 2

3.2.1 Compound and secondary patents 3

3.2.2 Patents on combinations 5

3.2.3 Impact of patent protection in producing and importing countries 5

3.2.4 Impact of uncertainty over patent status 5

3.2.5 Impact of licences 6

4 Methodology 7

4.1 Selection of FDCs for review 8

4.2 Sources of patent data 9

4.3 Sources of data on voluntary and compulsory licences 10

4.4 Sources of data on country-level procurement decisions 10

4.5 Sources of data on number of quality-assured suppliers 11

5 Overview of the patent situation for selected compounds and FDCs in Low and Middle Income Countries 11

5.1 Summary of patent status of individual compounds 11

5.2 Summary of licences over individual compounds 13

5.3 Analysis of patent status of FDC 15

5.3.1 Detailed case studies 20

6 Conclusions 24

1 Executive Summary

The use of fixed dose combinations (FDC) in antiretroviral therapy (ART) has several known advantages, particularly in resource-limited settings, both in terms of improved health outcomes and maximising value for money.

The present working paper analyses the extent to which there may be intellectual-property-related barriers to the development and greater uptake of affordable FDCs in low- and middle-income countries (LMICs). It provides an overview of such potential barriers with respect to three types of FDCs, namely, those that are already on the market, those that are currently under development, and those that could potentially be developed in light of WHO's current treatment guidelines. It includes 75 countries for which patent data was available, accounting for approximately 85% of people living with HIV.

According to the analysis in this paper, of the 11 WHO-recommended FDCs that are currently on the market, there may be patent barriers for the procurement of generic versions in certain LMICs in relation to 9 of them. Further, there appear to be patent barriers in a several LMICs for the use of all FDCs that are currently under development.

The analysis conducted offers four broad conclusions: (1) patents on individual compounds, on various secondary features of those compounds, or on combinations of compounds, may pose significant challenges to the development and uptake of existing and future FDCs in many LMICs; (2) the potential barriers vary between FDCs, and are stronger in relation to FDCs that are currently under development (i.e. for the next generation of products) but also exist in relation to existing FDCs; (3) the lack of publicly available, fully searchable and regularly updated information regarding patent status in many countries creates significant legal uncertainty regarding countries' ability to produce or procure generic FDCs; and (4) despite the existence of potential patent barriers to the uptake of FDCs, licences and other mechanisms have made it possible to overcome such challenges for certain products in some countries, but not for others. More widespread public-health oriented licensing, such as through a mechanism like the Medicines Patent Pool, would be important to overcome intellectual-property related barriers to the development and use of FDCs.

2 Introduction and Scope of the Paper

The present working paper[1] provides an overview of the intellectual property (IP)-related challenges to the development and uptake of fixed-dose combinations (FDC) in 75 low- and middle-income countries (LMICs) for which patent data was available. An FDC comprises two or more active ingredients combined into a single dosage form. The paper focuses on World Health Organization (WHO)[2]-recommended FDCs that are currently on the market as well as those that are under development or that could potentially be developed given WHO's 2010 treatment guidelines.

The scope of the paper is limited to IP-related challenges in LMICs. Other potential challenges to the development or uptake of FDCs, or IP-related challenges in high-income countries, are beyond the scope of this working paper.

3 Fixed Dose Combinations, ARVs and Patents

3.1 Benefits of FDCs in antiretroviral treatment

Treating HIV with FDCs has several known advantages, particularly in resource-limited settings, as has been recognised by the WHO for at least a decade[3]. Single-tablet FDCs "improve the reliability and security of supplies, reduce the number of pills, simplify the dosing regimen, are easier to take, enhance adherence, reduce the potential for inappropriate sharing of drugs and ensure that the correct dosage of each component is taken" (Nachega, et al 2011). In addition, ARVs formulated as FDCs have been shown to be consistently cheaper than the sum of the price of each individual component, thus offering significant potential cost savings when treatment regimens are procured as FDCs (Waning, et al 2010*a*). WHO treatment guidelines recommend that national treatment programmes take into account whether a particular regimen is available as an FDC when choosing among various recommended regimens of similar efficacy (WHO, 2010).

3.2 Impact of patents on accessibility of ARV FDCs

One of the first triple combination FDCs for HIV treatment was developed by the Indian generic pharmaceutical company Cipla in 2001.[4] This triple combination ARV regimen, comprised of stavudine, lamivudine and nevirapine, became a key component of the massive scale-up of antiretroviral treatment in the developing

---

[1] The paper is based on a report prepared for the Global Fund Market Dynamics and Commodities (MDC) Ad Hoc Committee in September 2011

[2] See, WHO (2010)

[3] See, for example, WHO, *Essential Medicines: WHO Model List* (2002) and WHO, *Scaling up Antiretroviral Therapy in Resource-Limited Settings* (2002).

[4] Hindu Business Line (2001) http://hindu.com/businessline/2001/08/07/stories/020751zb.htm

world in the years following. In developed countries, three separate originator companies (Bristol Myers Squibb[5], GlaxoSmithKline (now ViiV Healthcare) and Boehringer Ingelheim) held the patents on each component of this FDC. However, because India at the time did not grant product patents on pharmaceuticals, Cipla and other Indian pharmaceutical manufacturers were able to freely combine these and other ARVs into FDCs and export them to other countries where there were no patents in force. By 2011, the robust competition among these producers resulted in a 99% reduction in the price of the most widely used first line regimen from the price of the equivalent originator products in 2001 (MSF 2011).

However, the global intellectual property landscape has changed significantly since 2001. In 2005, India amended its Patents Act to come into compliance with its obligations under the TRIPS Agreement. With developing countries now legally bound under the TRIPS Agreement to make available product patent protection on pharmaceuticals[6], the ability of developing countries to manufacture or procure FDCs has become more uncertain. Moreover, the future ability of major generic manufacturers to make FDCs combining newer, more broadly patented ARVs, is far from certain.

An FDC, by definition, comprises two or more active ingredients combined into a single dosage form. A patent on a single compound contained in an FDC may block the generic production of the entire FDC, even if the other compound(s) are not patented. In many jurisdictions, subsequent patents relating to various secondary features of each compound, or covering the combination itself, may pose barriers to generic production. Difficulty in obtaining even the most basic information relating to whether a patent is in force in a developing country adds an additional layer of complexity that may result in sub-optimal procurement or production decisions. The following provides a brief summary of the types of patent-related challenges that may exist as they relate to the ability of countries to produce or procure lower-cost generic FDCs for HIV treatment.

3.2.1 Compound and secondary patents

Each compound in an FDC may be covered by a patent relating to the active ingredient itself. This form of patent protection, where it exists, represents the most significant barrier to generic production, as "they are infringed by making the drug product, almost by definition; otherwise bioequivalence is lacking" (Hemphill & Sampat 2011). However, for several of the older ARVs recommended by the WHO, the compound patent has expired, is nearing expiry, or was never granted in countries that did not permit the patenting of pharmaceutical products. This list

---

[5] The main patent claiming d4T was owned by Yale University and exclusively licensed to BMS.

[6] A key exception is least-developed countries (LDCs) that may choose to take advantage of an extension of the transition period to introduce pharmaceutical product patents until at least 2016.

includes, for example, abacavir, lamivudine, emtricitabine, zidovudine, tenofovir[7] and nevirapine.

The expiry of the compound patent, however, may not always clear the path for immediate generic production. Pharmaceutical companies regularly file for and obtain subsequent patents on various secondary features of a drug. An inquiry by the European Commission in 2009 concluded that "filing numerous patent applications for the same medicine... is a common practice," and that "an important objective of this approach is to delay or block the market entry of generic medicines" (European Commission 2009). This appears to be an increasing trend in the pharmaceutical industry; a recent study showed that in the United States, drugs approved from 2000 to 2002 have an average of 3.9 patents per drug, as compared to an average of 1.9 patents per drug among those approved between 1985 and 1987 (Hemphill and Sampat 2011).

These "secondary" patents do not cover the active molecule itself, but various other features of a drug, for example: a particular salt form, a specific dosage form, or a process of manufacturing the drug (European Commission 2009). The form of protection conferred by these secondary patents are often not as strong as that offered by the compound patent, as generic competitors may be able to "design around" the patents to avoid infringement (e.g., developing an alternative salt form of the drug, or by manufacturing the drug through a non-infringing process). In addition, many of these types of secondary patents may be subject to challenge on the grounds that they do not meet the basic criteria for patentability (Correa 2007*a*). Data from the United States suggests that such challenges are often successful (Hemphill and Sampat 2011).

Still, even where a compound patent does not exist or has expired in a particular jurisdiction, there may nonetheless be a legal risk of infringing one or more secondary patents that are in force. The question of whether it is possible for a generic competitor to "design around" a particular secondary patent, or whether such a patent is vulnerable to challenge in a country requires a highly technical case-by-case analysis of, among other things, the nature of the specific underlying technology, the scope of the patent claims, and the laws of the particular jurisdiction. As such, it is impossible to say as a general matter whether or not the presence of a secondary patent represents an actual obstacle to generic production and procurement. Precisely due to the highly technical nature of this evaluation and the time and cost of challenging secondary patents in each country where they may have been granted, the mere existence of these patents can potentially deter the production or procurement of a generic FDC even where the production or procurement of the FDC would not actually infringe the patent.

---

[7] The first patent claiming the tenofovir compound was filed by the Academy of Sciences of the former Czechoslovakia in 1986, mostly in developed countries.

3.2.2 Patents on combinations

A specific type of secondary patent is of special relevance in the evaluation of whether an FDC can be produced and procured as a generic: patents that cover the combination or a subset of the combination that is required in an FDC. In some cases, a patent covering the specific combination of an FDC may be in force even where the patents on the individual compounds have expired. For example, although the compound patents for AZT (zidovudine) and 3TC (lamivudine) have individually expired, patents covering the combination of these two products (alone or with a third component) are in force in some LMICs. Depending on the breadth of the claims, such a patent may pose an obstacle to the procurement of a generic FDC of AZT/3TC, as well as the triple FDC of AZT/3TC/ABC or AZT/3TC/NVP. The two patents covering the combination of AZT/3TC are due to expire in 2012 and 2017.

Patents on combinations represent a potentially significant challenge to the manufacture and procurement of the generic FDC, as it would be difficult to design around a patent covering the specific combination required in the FDC. These combination patents, like many other secondary patents, may be vulnerable to legal challenge (Correa 2007*a*; UNDP 2010*b*), but to the extent that they are valid and in force in a country, may pose an additional obstacle to generic access.

3.2.3 Impact of patent protection in producing and importing countries

An additional layer of complexity must be taken into account in countries with insufficient domestic capacity to manufacture ARVs. Relatively few countries have the ability to manufacture ARVs domestically. These countries must thus import their ARVs from countries with the ability to make and export these drugs. For ARVs, the role of India takes special significance, as its generic manufacturers supply over 80% of ARVs taken in the developing world (Waning et al 2010*b*). Where a country imports its ARV FDCs, the patent status of each component of the FDC, as well as potential patents covering the FDC itself, must be evaluated in both the importing country and the exporting country of manufacture. Even if there are no patent barriers in the importing country, the existence of even a single patent on just one component of an FDC in the country of manufacture could potentially be sufficient to prevent the generic supply of the entire FDC to the importing country.

3.2.4 Impact of uncertainty over patent status

Compounding the complexities discussed above is the fact that patent information relating to an FDC is often difficult, if not impossible, to obtain in many LMICs. Only some developing country patent offices have publicly available, fully searchable and regularly updated databases that can provide accurate information relating to the status of a pending application or the existence of a patent. In the face of such uncertainty, there is a risk that a more expensive patented version of a product will be procured, even where there are in fact no patent barriers to the purchase of a generic version in a country. Indeed, given that some FDCs are available only as

generics (e.g., TDF/3TC/EFV or ATV/r), such uncertainty could lead to the decision to forego the procurement of the FDC altogether.

3.2.5 Impact of licences

Even where there are patents over one or more of the active ingredients in an FDC or over the combination, licences may have been issued that authorise the manufacture or supply of a generic FDC in certain countries. Licences may be of a voluntary or a compulsory nature. In the case of a voluntary licence, the patent holder authorises the licensee to perform certain acts, such as manufacture and sell a patented invention, under certain terms and conditions. This may include the payment of a royalty and may include a number of restrictions, including on the countries covered by the licence. Compulsory licences are granted by a government to an entity other than the patent holder to produce, import or sell a given product that is patented, in exchange for "adequate remuneration."

In order to get a better understanding of the extent to which the existence of a patent on certain compounds represents an actual barrier to the manufacture or supply of a generic version of an FDC, it is important to know whether those patents have been the subject of a licence and what is and is not allowed under those licences.

3.2.5.1 Voluntary licences[8]

Many originator ARV companies engage in voluntary licensing activities that allow for one or more generic manufacturers to make and sell a patented HIV medicine under a number of terms and conditions. Industry practices vary widely on this, with differences in, for example, geographical scope, royalty obligations, and the number and identity of licensees. Other restrictive terms can potentially be included in the licences that have an adverse impact on the ability of generic licensees to manufacture and sell freely, including, for example: restrictions on the FDCs that may be manufactured, or restrictions on the ability of the generic manufacturer to make its own active ingredient. However, due to the lack of publicly available information on the precise terms and conditions of most voluntary licences, a full analysis cannot be conducted.[9]

---

[8] For the purposes of this report, "non-assert declarations" (issued by Boehringer-Ingelheim) and "immunity-from-suit agreements" (issued by Bristol Myers-Squibb) will be treated under the category of voluntary licences. Although voluntary licences, non-assert declarations and immunity-from-suit agreements have some key differences, for the purposes of this report, they are functionally identical in that they provide legal certainty for the generic manufacturer that it will not be sued for patent infringement under certain pre-defined terms and conditions.

[9] An exception to this are the licences negotiated through the Medicines Patent Pool, which makes all licence agreements publicly available on its website. See http://www.medicinespatentpool.org/LICENSING/Current-Licences

Due to the differences in voluntary licensing practices by different originator companies the existence of a voluntary licence for one or more compound in an FDC may not allow for the FDC itself to be manufactured, or may allow the FDC to be made available in some countries, but not others. Information that is publicly available on the voluntary licences relating to ARVs is provided in the Section 5.2.

3.2.5.2 Compulsory licences

In addition to voluntary measures such as those described above, countries have the right under the TRIPS Agreement to issue compulsory licences, provided that certain procedures are followed (Love 2001; WTO 2006). In 2001, WTO Members agreed to the Doha Declaration on the TRIPS Agreement and Public Health, which (among other things) expressly recognised that each "Member has the right to grant compulsory licenses and the freedom to determine the grounds upon which such licenses are granted." Information on some of the compulsory licences that have been issued is provided in section 5.2.

The Doha Declaration also recognised that the right of member countries to issue compulsory licences was not particularly helpful to those countries with insufficient domestic manufacturing capacity, due to restrictions in TRIPS on export of products made under a compulsory license. On 30 August 2003, the WTO General Council issued a decision (the 30 August Decision) intended to remedy this situation.[10] Thus far, only a handful of potential exporting members have implemented the 30 August Decision into their national laws, and there has only been one instance in which the 30 August Decision has been used to export drugs under a compulsory licence to a country with insufficient manufacturing capacity.[11]

The existence of one or more compulsory licences may, therefore, also impact on the possibility of a generic version of an FDC being made or sold in a given country.

4 Methodology

In order to determine the extent to which patents represent challenges for access to FDCs, an analysis was conducted, involving: (1) a selection of FDCs for review, based upon current WHO recommendations and public information on the FDCs that are

---

[10] Decision of the General Council of 30 August 2003, Implementation of Paragraph 6 of the Doha Declaration on the TRIPS Agreement and Public Health. The "temporary waiver" of the Decision was made into a permanent amendment to TRIPS in December 2005, under a new Article 31bis. The amendment will become part of TRIPS upon ratification by at least two-thirds of the WTO members.

[11] In September 2007, Canada issued a compulsory licence under its legislation implementing the 30 August Decision for export of a triple fixed-dose ARV combination to Rwanda. See Rwanda Notification Under Paragraph 2(a) of the Decision of 30 August 2003 on the Implementation of Paragraph 6 of the Doha Declaration on the TRIPS Agreement and Public Health, WTO IP/N/9/RWA/1.

under development; (2) a review of the Patent Status Database for Selected HIV Medicines, available at the Medicines Patent Pool website, to determine whether any patents are pending or in force in the 75 LMICs included in the database; (3) a review of publicly available sources of information to determine whether any voluntary or compulsory licences were in effect for a given ARV or FDC in a specific territory; and (4) a review of country-level procurement data obtained from WHO's Global Price Reporting Mechanism. Each step of the analysis is described below.

4.1 Selection of FDCs for review

For the purposes of this analysis, the FDCs identified in Table 1 have been considered. In the first category, we have included FDCs that are recommended by the 2010 WHO treatment guidelines and for which there is currently at least one supplier. This includes 11 FDCs and will be referred to hereafter as Category 1 FDCs. Secondly, are FDCs that are known to be currently under development, submitted for regulatory approval, or very recently approved (but not yet recommended), based on the public sources consulted for this paper. This includes 7 FDCs and will be referred to as Category 2 FDCs. Lastly, are FDCs that could potentially be developed based on current WHO recommendations. Several combinations could be included in this latter category, including some that may only be possible as co-blister packs. For illustrative purposes, we have included only 4 combinations in Category 3, and a more complete list is available from a joint document prepared by the Medicines Patent Pool, UNITAID and WHO (and endorsed by a large number of partners of the WHO/UNAIDS Treatment 2.0 initiative) that was submitted to the WHO Expert Group on the Selection and Use of Essential Medicines.[12]

A fourth category, which has not been included in this paper, is that of combinations that are currently not under development and that are not currently recommended but that may hold potential. This may include, for example, combinations including new pipeline products.[13] It is important to note that the existence of intellectual property rights over one or more compound in a possible FDC is one of the reasons why certain co-formulations (FDCs or co-blisters) may not have been developed.

---

[12] A full list of FDCs and/or co-blister packs that would meet WHO recommendations is available in the document submitted to the WHO Expert Committee on the Selection and Use of Essential Medicines available at:
http://www.who.int/selection_medicines/committees/expert/18/policy/policy4/en/index.html

[13] See, for example, combinations with dolutegravir proposed by Boyd (2011)

Table 1: FDCs by Category

Category 1	Category 2	Category 3
ABC/3TC	TDF/FTC/ELV/COB	DRV/r
ABC/3TC/NVP	ABC/3TC/DLG	TDF/3TC/NVP (QD)
AZT/3TC	LPV/r/3TC[15]	ETV +RAL +DRV/r
AZT/3TC/NVP	TDF/FTC/RIL[16]	TDF/FTC/ATV/r
AZT/3TC/ABC	DRV/COB[17]	
TDF/3TC	ATV/COB[18]	
TDF/FTC	GS-7340/FTC/DRV/COB[19]	
TDF/3TC/EFV		
TDF/FTC/EFV		
LPV/r		
ATV/r[14]		

4.2 Sources of patent data

Once the target FDCs (and the individual compounds necessary for these FDCs) were identified, an analysis of the patent status was conducted using the Patent Status Database for Selected HIV Medicines, publicly available on the Medicines Patent Pool website.[20] The Patent Status Database provides information on the patent status of some key patents on selected ARVs in 75 LMICs from a total of 40 national and regional patent offices.

The data made available in the database was obtained from and cross-checked between a variety of sources, including many local patent offices that agreed to make this information available via the World Intellectual Property Organization (WIPO). However, the information in the database should not be considered a complete and authoritative source of patent information on ARVs. It provides a snapshot at a particular point in time based on the information that was available to the Medicines Patent Pool.

---

[14] Approved by the US Food and Drug Administration in November 2011: http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm280673.htm

[15] See: http://www.abbott.com/press-release/2011-july15.htm

[16] Approved by the US Food and Drug Administration in August 2011 http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm267592.htm

[17] See: http://www.gilead.com/pr_1580287

[18] See: http://www.gilead.com/pr_1621754

[19] See: http://investors.gilead.com/phoenix.zhtml?c=69964&p=irol-newsArticle&ID=1630785&highlight=

[20] Available at: http://www.medicinespatentpool.org/patent/search

One key limitation of the data is that it does not identify all relevant patents or patent applications that may exist for a given ARV or FDC. As mentioned, there are often a large number of applications for secondary patents that are filed for and granted. Additionally, given the dynamic nature of the patent prosecution and maintenance process, there is the possibility that the status of a given patent or patent application may have changed since the last time it was updated. For example, a patent that appears as "granted" or a patent application that appears as "filed" may have expired or lapsed, or may have been withdrawn, rejected, amended, revoked or opposed.

Finally, although the Patent Status Database is, as far as we are aware, the most comprehensive collection of patent status information of ARVs in LMICs, there are a large number of countries for which the database has incomplete information, or no information at all. The Medicines Patent Pool, in cooperation with WIPO, national patent offices, and others, is working to expand the number of countries for which patent information is available.

4.3 Sources of data on voluntary and compulsory licences

Information on voluntary and compulsory licences was compiled from a number of publicly-available sources, including patent-holder websites, government websites, news sources, and reports compiled by experts. However, it should be noted that the information is incomplete in several respects: for nearly all voluntary licences, many key terms and conditions are kept confidential and cannot be independently verified.

For compulsory licences, many governments have issued government use orders through procurement letters, but detailed information on these letters is not publicly available; one study of such letters found that over 60 countries had made use of TRIPS flexibilities to access generic medicines, but does not provide details regarding the specific medicines or dates of validity ('t Hoen 2009). In addition, it is unclear whether some compulsory licences, especially those that were issued several years ago, are still in effect.

4.4 Sources of data on country-level procurement decisions

Country level procurement data was gathered through the World Health Organization's Global Price Reporting Mechanism (GPRM), a web-based database containing information on donor-funded procurement of commodities, including those for HIV/AIDS; data is available on ARV procurement from 2003 to the present.[21] This information was used to determine whether, and to what extent, LMICS were procuring generic products despite the potential existence of a patent barrier. It is important to note, however, that procurement data from many countries are not included in the database.

---

[21] Available at: http://apps.who.int/hiv/amds/price/hdd/

4.5 Sources of data on number of quality-assured suppliers

Information on the number of quality-assured suppliers was obtained from the website of the WHO Prequalification Program. For the purpose of this document, quality assured sources refer to those compliant with the Global Fund's Quality Assurance Policy.

5 Overview of the patent situation for selected compounds and FDCs in Low and Middle Income Countries

5.1 Summary of patent status of individual compounds

The following provides a summary of the patent status of individual compounds that are part of the FDCs included in Categories 1, 2 and 3 as defined above

Abacavir (ABC): The compound patent for abacavir appears to have expired in 2010 in many countries. There are, however, secondary patents, such as those on the hemi-sulfate salt and the oral solution for paediatric use, which are either pending or granted in several LMICs.

Atazanavir (ATV): Compound patents on ATV are either granted or pending in several jurisdictions, including key producing countries (e.g. AR, BR, CN, IN, KG, MY, PH, TJ, TH) A formulation patent on the bisulfate salt and a process patent have been filed or granted in many LMICs.

Cobicistat (COB): Cobicistat is an investigational pharmacokinetic enhancer and is in phase III clinical trials. Compound and formulation patents on cobicistat have been filed and are pending in many LMICs, including, for example, AR, ARIPO, BR, CN, EAPO, IN, MO, MX, OAPI, VN and ZA.

Darunavir (DRV): Patents on DRV appear to be in force in few LMICs, including, for example, BR, CN, MX and VN. There are a number of other patents relating to DRV, including on a pseudopolymorph, a preparation of key intermediates and on the combination with ritonavir, that might potentially act as a barrier to production or sale of generic versions in some additional countries (e.g. pseudopolymorph patent granted in African countries that are members of ARIPO).

Dolutegravir (DLG or GSK-572): DLG is an investigational integrase inhibitor and is in phase III clinical trials. The compound patent has been granted or is pending in many LMICs, including AM, ARIPO, CN, CO, EAPO, IN, ID, OAPI, PH, RU and ZA. There is also a process patent and a patent on an intermediate, which have been filed in many countries.

Efavirenz (EFV): Compound patents on efavirenz are in force in a few LMICs, namely, AR, BR, CL, CN, TH, UA and ZA based on available information and are likely to expire in 2012 or

2013. There do not appear to be any compound patents in most other LMICs for which information is available. No information is currently available on other patents, such as formulation patents for EFV, although patents on EFV in combination with TDF and FTC are pending in many jurisdictions.

Elvitegravir (EVG): EVG is an investigational integrase inhibitor in phase III clinical trials. There are compound patents granted or pending on EVG in several LMICs, including AR, BR, CL, CN, CO, IN, MY, MX, PE, PH, RU, VN and ZA. There are also formulation patents on the crystal form.

Emtricitabine (FTC): The compound patent for emtricitabine appears to have expired in many countries in 2010. There are, however, some formulation patents, which have been granted in several countries with Global Fund grants.

Etravirine (ETV): There are compound patents granted or pending on ETV in many developing countries including ARIPO, AM, AR, BR, CL, CN, EAPO, ID, KG, MY, MX, OAPI, PH, RU, TJ, UA, VN and ZA. There are also patents on new forms, which have also been filed in many countries.

GS-7340: This is a prodrug of tenofovir that is currently under development (phase II). No patent status information was available at the time of preparing this paper.

Lamivudine (3TC): The compound patents on 3TC appear to have expired in 2010 in many countries. There are formulation patents on the crystal form and on a new formulation, which have been granted in several LMICs. There are many generic versions of 3TC, alone or in combination, on the market and there appear to be limited patent barriers on its production or sale of the single-ingredient product.

Lopinavir (LPV): The compound patents on LPV appear to be pending or granted in some countries, including, AR, BR, CN, CO, MX, PH, TH and ZA. In addition, there are patents on LPV/r as soft gel caps and as a tablet formulation, which are patented in many developing countries.

Nevirapine (NVP): The compound patents appear to have expired in 2010 in most countries. There are, however, formulation patents, such as those on the hemihydrate formulation or the extended release formulation, which have been filed or granted in many countries.

Rilpivirine (RIL): RIL received regulatory approval in early 2011. There are compound patents that cover RIL that are granted or pending in a large number of countries, including AR, ARIPO, BR, CL, CN, IN, JO, LK, MX, MY, OAPI, PA, PH, UA, VN and ZA. There are also patents on salt forms of rilpivirine that have been granted or are pending in many developing countries.

Ritonavir (RTV): Compound patents on RTV appear to be in force in few LMICs (e.g. MX and PH). There are, however, formulation patents on the crystalline polymorph that are pending or granted in a number of middle-income countries. There are also patents that cover the combination with LPV and/or other protease inhibitors in a number of jurisdictions.

Tenofovir Disoproxil Fumarate (TDF): The original patent on tenofovir has expired, but there are patents covering the disoproxil prodrug and/or the fumarate salt in a few jurisdictions (e.g. CN, ID, MX). A process patent has been granted in India and other patents are pending while others have been rejected. Patents on the combination with FTC, EFV and RIL are also granted or pending in several countries.

Zidovudine (AZT): The main patent on AZT expired in 2006 and the product is widely available as a generic. There do not appear to be any patent barriers for the compound as a stand-alone product. There are, however, patents in certain developing countries on AZT combined with other compounds.

5.2 Summary of licences over individual compounds

The following provides a summary of the voluntary licences (table 2) and compulsory licences (table 3) for which there is public information.

Table 2: Summary of known existing voluntary licences on relevant ARVs

	Number of licensees	Geographical Scope	Comments
Abacavir*	Several (exact number unknown)	Sub-Saharan Africa, Low Income Countries (LIC) and LDCs (69 countries)	- Compound patent generally expired but licence likely includes formulation patents - Detailed terms and conditions are confidential
Atazanavir*	Four	Sub-Saharan Africa and India (47 countries)	- Structured as immunity-from-suit agreements - Detailed terms and conditions are confidential
Cobicistat	Several (all based in India)	103 countries and semi-exclusive licences covering an additional nine countries	Licence granted to the Medicines Patent Pool is public
Darunavir	Two	Sub-Saharan Africa, LDCs and India	- The licence appears to provide the right to register, distribute and package (but not manufacture) for one company and for manufacturing the formulation (not the active pharmaceutical ingredient) to another - Detailed terms and conditions are confidential
Dolutegravir* (also known as GSK 572)	-	-	- While a commitment to license was announced in July 2010, no licence appears to have been granted to date
Efavirenz	Five	South Africa and 10 other countries in Sub-Saharan	- Detailed terms and conditions are confidential

	Number of licensees	Geographical Scope	Comments
		Africa	
Elvitegravir	Several (all based in India)	100 countries and semi-exclusive licences covering 9 additional countries	- Licence granted to the Medicines Patent Pool is public
Emtricitabine	13 licensees	112 countries	- Structured as an immunity-from-suit agreement in tenofovir license - Licence granted to the Medicines Patent Pool is public
Etravirine	Two	Sub-Saharan Africa	- Licence is for registration and distribution (not manufacturing) - Detailed terms and conditions are confidential
GS-7340	None	-	- Compound still in phase II and no licences available as yet
Lamivudine*	Several (exact number unknown)	Sub-Saharan Africa, LICs and LDCs (69 countries)	- Compound patent expired but licence likely includes formulation patents - Detailed terms and conditions are confidential
Lopinavir	None	-	- No licence has been publicly announced on this product
Nevirapine*	Several (exact number unknown)	Africa, LICs and LDCs (78 countries)	- Structured as non-assert declarations
Raltegravir	Two	Sub-Saharan Africa and LICs	- Very limited public information about these licences
Rilpivirine	Five	Expanded in late 2011 to include 112 countries	- Detailed terms and conditions are confidential
Ritonavir	None	-	- No licence has been publicly announced on this product
Tenofovir	13 licensees	112 countries	- Licence granted to the Medicines Patent Pool is public
Zidovudine*	Several (exact number unknown)	Sub-Saharan Africa, LICs and LDCs (69 countries)	- Compound patent expired but licence likely includes formulation patents - Detailed terms and conditions are confidential

* Indicates compounds which are the subject matter of current negotiations with the Medicines Patent Pool

Sources: Websites of companies and public information

Table 3: Summary of known compulsory licences on relevant ARVs

2002	Zimbabwe	ARVs (various)
2003	Malaysia	AZT, 3TC/AZT
2004	Zambia	3TC, NVP
2004	Indonesia	3TC, NVP

2004	Mozambique	3TC, NVP
2004	Swaziland	ARVs (various)
2005	Guinea	ARVs (various)
2005	Ghana	ARVs (various)
2005	Eritrea	ARVs (various)
2006-08	Thailand	EFV, LPV/r
2007	Indonesia	EFV
2007	Brazil	EFV
2007	Canada (for export to Rwanda under WTO Aug 30th Decision)	AZT/3TC/NVP
2010	Ecuador	RTV

5.3 Analysis of patent status of FDC

The analysis that follows draws information from the preceding sections and seeks to summarise the potential IP-related challenges that may exist with respect to the three categories of FDCs that are being considered in this paper. The main focus is on the extent to which patents on individual compounds in the FDCs, or on the combinations, may constitute barriers to the development or uptake of the FDCs, taking into account existing (voluntary and compulsory) licences. Wherever possible, potential challenges relating to both the production and the sale/importation of the FDCs have been mentioned. The tables draw from the publicly available sources described above.

A more detailed analysis of three specific FDCs based on publicly available information is provided in the following section.

Table 4: Patent Status of Category 1 FDCs

FDCs Category 1	IP-Related Challenges
ABC/3TC and ABC/3TC/NVP	- There are three quality-assured producers[22] for this FDC (only two for the paediatric formulation) - Compound patents for all three compounds have generally expired in most developing countries - Formulation patents for ABC (hemi-sulfate salt and oral solution for paediatric salt), for 3TC and for NVP (hemihydrate formulation) may pose barriers in some jurisdictions, depending on local patentability standards - In countries where patents on ABC formulations are in force and that are not included in the ABC licence, there may be barriers to the procurement of the generic FDC
AZT/3TC and AZT/3TC/NVP	- There are many quality-assured products of these FDCs on the market - Patents for all three compounds have expired - There are some secondary patents that might possibly act as a barrier in countries not covered by either the licences or agreements not to sue on the various individual compounds - Combination patents on AZT/3TC have also been granted in some countries - In practice, however, there appear to be limited intellectual property barriers on these FDC
AZT/3TC/ABC	- There are four quality-assured suppliers for this FDC currently on the market - Patents for all three compounds have expired - Secondary patents, particularly for ABC, could act as a barrier for the production or sale of the product in countries not covered by the ABC licence - Combination patents on AZT/3TC have also been granted in some countries
TDF/FTC[23] and TDF/3TC	- There are five quality-assured products on the market for these two FDCs - Compound patents on FTC have expired and patents on TDF have been granted in a few LMICs (CN, MX and ID, but the latter is covered by TDF licences) - Secondary patents on FTC and a process patent for TDF in India could potentially be a barrier in countries not covered by TDF and FTC licences, depending on local patentability standards and processes used by generic manufacturers - A patent on the TDF/FTC combination has been filed and granted in many developing countries and might also be a barrier to production or sale of generics - Sale of FDC by some suppliers may be limited to countries covered by

[22] For the purpose of this document, quality assured sources refer to those compliant with the Global Fund's Quality Assurance Policy

[23] In line with the WHO treatment guidelines, FTC and 3TC have been treated as interchangeable for this analysis, as their patent situation also appears to be fairly similar (compound patent expired and some formulation patents in developing countries)

FDCs Category 1	IP-Related Challenges
	licences on TDF
TDF/FTC/EFV and TDF/3TC/EFV	- There are three quality-assured suppliers for TDF/FTC/EFV; and one for TDF/3TC/EFV - Product patents for at least one of the compounds in a limited number of LMICs (e.g. AR, CL, CN, MX, UA) could be potential barriers for generic production or sale in those countries - Formulation patents on FTC and a process patent for TDF in India could potentially be a barrier in countries not covered by TDF/FTC licences, depending on local patentability standards and processes used by generics - Patents on the triple combination and the TDF/FTC combination have also been filed in many countries and granted in a few and may potentially act as a barrier, depending on local patentability standards - Sale of FDC by some suppliers may be limited to countries covered by licences
LPV/r	- There are currently four quality-assured products on the market - Patents for at least one of the compounds of this FDC are granted or pending in some countries (AR, BR, CN, CO, EC, MX, PH, TH and ZA) - Compulsory licences have been issued in some countries for this product or combination - Patents on the LPV/r soft-gel caps and tablet formulations have also been granted or are pending in a number of additional developing countries, which may act as barriers to production or sale in some countries (e.g. AM, AZ, DO, GE, GT, KG, LK, RU, TJ, UA) - No voluntary licences on this FDC or its components have been publicly announced
ATV/r	- There is currently only one supplier for this FDC - Patents granted or pending for at least one compound may act as a barrier to generic competition in some LMICs (e.g. AR, CN, KG, IN, MX, MY, PH, TJ, TH) for which no licences appear to be currently available. This includes several key producing countries. - Secondary patents (e.g. ATV bisulfate salt or RTV crystalline polymorph) could be a potential barrier, depending on local patentability standards - There are also patents on RTV combined with protease inhibitors in many countries - Sale of FDC may be limited to countries covered by the ATV licences (47 countries)

Table 5 – Patent Status of Category 2 FDCs

FDCs Category 2	IP-Related Challenges
TDF/FTC/EVG/COB	- Product known as "the Quad" is currently in phase III clinical trials - Compound patents for COB and EVG generally pending (or granted) in many countries (e.g. AM, ARIPO, CN, CO, EAPO, IN, ID, OAPI, PH, RU and ZA), including key producing countries - Licences granted to several Indian licensees for COB, EVG and the Quad in 103, 100 and 100 countries, respectively, through the Medicines Patent Pool - Possible barrier to production of generics outside of India and for sale in countries not covered by the licences, if pending patents for EVG and COB are granted
ABC/3TC/DLG	- Combination currently under development and includes investigational integrase inhibitor DLG - Patents on DLG (compound, processes and intermediates) have been filed or granted in a large number of LMICs, including main producing countries - Secondary patents on ABC (hemisulfate salt and composition for paediatric use) also granted in some countries - Patents on DLG as well as formulation patents on ABC and 3TC could potentially act as a barrier to production or sale for this FDC
LPV/r/3TC	- Combination announced as being under development - Patent information and potential challenges relating to this FDC are similar to those explained above for LPV/r
DRV/COB	- Combination announced as being under development - Compound patents pending in many countries for COB and some secondary patents have been granted for DRV - Possible barrier to production of generics outside of India and for sale in countries not covered by the COB licenses
TDF/FTC/RIL	- Combination recently obtained regulatory approval from the US FDA (no generic suppliers yet) - Compound patents on RIL have been filed or granted in many developing countries, including most key producing countries - More limited patent coverage for TDF and FTC - Expansion of licence on RIL to 112 countries announced in late 2011. Likely barriers for production and sale of RIL in countries outside those territories - Combination patents on TDF/FTC and for TDF/FTC/RIL have been filed in many LMICs, including many not covered by existing voluntary licences
ATV/COB	- Combination announced as being under development - Compound patents pending in many jurisdictions for COB and patents granted or pending in a number of jurisdictions for ATV. - Limited information on any combinations patents that may cover ATV/r or more generally ritonavir in combination with any protease inhibitor (likely from country to country depending on patentability standards and the claims granted for individual patents)
GS-7340/FTC/DRV/COB	- Combination under development - While there are limited patent barriers relating to FTC and DRV, patents are pending in many countries for COB. - Patent status of GS-7340 is not known

Table 6 – Patent Status of Category 3 FDCs[24]

FDCs Category 3	IP-Related Challenges
DRV/r	- Not currently on the market but recommended by WHO as part of a possible third-line regimen - Patents for at least one compound appear to be in force in some countries, including BR, CN, MX, PH and VN, which are not covered by existing licences - Secondary patents could act as barriers in some additional countries depending on local patentability standards - There are also patents on RTV in combination with protease inhibitors that have been filed or granted in many countries
ETV +RAL + DRV/r	- An FDC or co-blister pack for third-line currently does not exist - While it may not be possible as an FDC, a co-blister pack could form part of a treatment regimen if clinically appropriate - Nevertheless, there appear to be strong patent barriers for a third-line generic regimen - Compound patents for ETV and for RAL have been granted in many countries including key producing countries - Voluntary licences for ETV and RAL appear to have a limited geographical scope (only for distribution in Sub-Saharan Africa (SSA) for ETV and for SSA and LICs for RAL) - Secondary patents on all four compounds have also been granted or are pending in many countries and could act as a barrier to generic production or sale
TDF/3TC/NVP (QD)	- Not currently on the market, but recent approval of extended release NVP could make this a potentially interesting combination for first-line (possibly as a co-blister pack) - Patents on TDF in a few countries (CN and MX) and a TDF process patent in India may pose barriers to generic competition - Patent on the NVP extended release formulation is pending in many jurisdictions (and granted in a few, e.g. South Africa) and could act as a barrier, if granted
TDF/3TC/ATV/r	- Not currently on the market as an FDC - Patents granted or pending for at least one compound may act as a barrier to generic competition in some LMICs (e.g. AR, CN, KG, IN, MX, MY, PH, TJ, TH) for which no licences appear to be currently available. This includes several key producing countries. - Secondary patents (e.g. ATV bisulfate salt or RTV crystalline polymorph) and on the combination TDF/FTC could be a potential barrier, depending on local patentability standards - There are also patents on RTV combined with protease inhibitors - Sale of FDC, if developed, may be limited to countries currently covered by the ATV licences (47 countries)

[24] Additional FDCs and/or co-blister packs that would meet WHO recommendations are available in document submitted to the WHO Expert Committee on the Selection and Use of Essential Medicines available at: http://www.who.int/selection_medicines/committees/expert/18/policy/policy4/en/index.html

5.3.1 Detailed case studies

In addition to the summary analyses above, we offer here detailed case studies of three FDCs to illustrate the ways in which compound patents, secondary patents (including combination patents), and licenses interact to create or overcome barriers to generic FDCs. Patent and licensing situations vary tremendously among compounds and FDCs; we chose these case studies to illustrate the breadth of issues that may arise, but these findings should not be extrapolated to all FDCs. We analysed the patent situation in the 126 countries that are recipients of active Global Fund grants (across all disease areas).[25]

Table 7: Existing first-line FDC recommended by WHO: TDF/FTC/EFV

1	Total number of countries with Global Fund grants	126
2	-In which some ARV patent data is available	75
3	-In which ARV patent data is not available, therefore patent situation is uncertain	51
4	-In which insufficient information is available to make a determination regarding TDF/FTC/EFV*	73
5	Of the 75 countries for which patent data is available, # of countries where *any*** patents exist on TDF, FTC, EFV, or any combination of these	43
6	----Of these 43, # of countries where relevant licences (either voluntary or compulsory) are available for the FDC	28
7	----Of these 43, # of countries where IP barriers to accessing the generic FDC may exist	15
7a	----Of these 15 where a barrier may exist, # of countries that seem to have overcome the barrier to purchase a generic version	1
8	Of the 43 countries where *any* patents exist on TDF/FTC/EFV, # of countries where at least one of these is a basic*** patent	9
9	----Of these 43, # of countries where combination patents have been granted	13
10	----Of these 43, # of countries where combination patents are pending	18

*this includes countries in which the status of one or more of the patents relevant to this FDC is unknown as well as countries for which no data is available in the Patent Status Database
**includes compound patent and any secondary patents (e.g. processes, salts, polymorphs, method of use) that are included in the Medicines Patent Pool Patent Status Database; includes patent applications filed or granted
***compound patents confer a stronger level of protection than secondary patents

[25] http://portfolio.theglobalfund.org/en/Home/Index (accessed in September 2011)

Table 8: Existing second-line FDC recommended by WHO: LPV/r

1	Total number of countries with Global Fund grants	126
2	-In which some ARV patent data is available	75
3	-In which ARV patent data is not available, therefore patent situation is uncertain	51
4	-In which insufficient information is available to make a determination regarding LPV/r*	74
5	Of the 75 countries for which patent data is available, # of countries where *any*** patents exist on LPV, r, or the combination of these	26
6	----Of these 26, # of countries where relevant licenses (either voluntary or compulsory) are available for the FDC	1
7	----Of these 26, # of countries where IP barrier to accessing the generic FDC may exist	25
7a	----Of these 25 where a barrier may exist, # of countries that seem to have overcome the barrier to purchase a generic	7
8	Of the 26 where *any* patents exist on LPV/r, # of countries where at least one of these is a basic *** patent	8
9	----Of these 26, # of countries where combination/formulation patents have been granted	16
10	----Of these 26, # of countries where combination/formulation patents are pending	3

*this includes countries in which the status of one or more of the patents relevant to this FDC is unknown as well as countries for which no data is available in the Patent Status Database
**includes compound patent and any secondary patents (e.g. processes, salts, polymorphs, method of use) for which information is included in the Medicines Patent Pool Patents Status Database; includes patent applications filed or granted
***compound patents confer a stronger level of protection than secondary patents

Table 9: FDC that is currently under development: ABC/3TC/DLG

1	Total number of countries with Global Fund grants	126
2	-In which some ARV patent data is available	75
3	-In which ARV patent data is not available, therefore patent situation is uncertain	51
4	-In which insufficient information is available to make a determination regarding ABC/3TC/DLG*	80
5	Of the 75 countries for which patent data is available, # of countries where *any*** patents exist on ABC, 3TC, DLG or the combination of these	72
6	----Of these 72, # of countries where relevant licences (either voluntary or compulsory) are available for the FDC	0
7	----Of these 72, # of countries where IP barrier to accessing the generic FDC may exist	72
8	Of the 72 where *any* patents exist on ABC/3TC/DLG, # of countries where at least one of these is a basic*** patent	57

CPHE - SOCH
Koramangala
Bangalore - 34

9	----Of these 72, # of countries where secondary**** patents have been granted	66
10	----Of these 72, # of countries where secondary patents are pending	6

*this includes countries in which the status of one or more of the patents relevant to this FDC is unknown as well as countries for which no data is available in the Patent Status Database
**includes compound patent and any secondary patents (e.g. processes, salts, polymorphs, method of use) for which information is included in the Medicines Patent Pool Patents Status Database; includes patent applications filed or granted
***compound patents confer a stronger level of protection than secondary patents
****this includes only formulation patents, but not any

The analyses above demonstrates how patents on various compounds in an FDC can have an additive effect. That is, patent barriers for an FDC can be multiple times what they may be for any single component within the FDC. A patent on any single compound within the FDC can be blocking, even if the other compounds in the combination are not patented. The problem is magnified even further due to the existence of combination patents. For example, for the combination of LPV/r, we found patents or pending patent applications on LPV in 8 countries and on RTV in 2 countries, but combination patents in 25 out of the 75 for which data was available. A summary table is provided below.

Table 9. Illustration of additive effect of patents within an FDC: Number of countries with any patent or patent application

TDF/FTC/EFV	TDF compound	FTC compound	EFV compound	Secondary patents (incl. combination patents)
Patents or patent applications	0	2	10	36
Total	43			
LPV/r	LPV compound	RTV compound	Secondary patents (incl. combination patents)	
Patents or patent applications	8	2	25	
Total	26			
ABC/3TC/DLG	ABC compound	3TC compound	DLG compound	Secondary patents (incl. combination patents)
Components	1	2	57	72
Total	72			

Further, the lack of information on patent status in many countries creates uncertainty and highlights the need to continue to enhance patent transparency in this field. In the three cases studied above it was not possible to make any preliminary assessment of the extent to which there may be patent barriers in many

countries (73, 74 and 80 respectively) given the lack of information on the patent status, including in many countries not covered by current licences.

6 Conclusions

The analysis conducted offers four broad conclusions:

(1) patents on individual compounds, on various secondary features of those compounds, or on combinations of compounds, may pose significant challenges to the development and uptake of existing and future FDCs in many LMICs;
(2) the potential barriers vary between FDCs, and are stronger in relation to FDCs that are currently under development (i.e. for the next generation of products) but also exist in some countries in relation to existing FDCs;
(3) the lack of publicly available, fully searchable and regularly updated information regarding patent status in many countries creates significant legal uncertainty regarding countries' ability to produce or procure generic FDCs; and
(4) despite the existence of potential patent barriers to the uptake of FDCs, licences and other mechanisms have made it possible to overcome such challenges for certain products in some countries, but not for others.

According to the analysis in this paper, of the 11 WHO-recommended FDCs that are currently on the market, there may be patent barriers for the procurement of generic versions in certain LMICs in relation to at least 9 of them. Further, there appear to be patent barriers in a number of LMICs for the development and use of all FDCs that are currently under development.

Lack of reliable patent data is problematic because of the considerable legal uncertainty it causes. Such uncertainty could deter cautious countries or international procurement agents from buying lower-cost generic versions of FDCs, even if in reality there are no blocking patents in a country. In a large number of LMICs, insufficient information was available to make a determination regarding the existence or extent of patent barriers: this was the case for 73 countries for TDF/FTC/EFV; 74 countries for LPV/r; and 80 countries for ABC/3TC/DLG. These gaps in publicly available patent information underscore the importance of continuously improving patent databases, and increasing the transparency of the patent system.

In addition, it may be challenging for procurement agents to obtain and accurately synthesise up to date information on patent status and relevant licences surrounding a particular FDC. Assessing the patent situation requires synthesising information regarding both compound patents and potentially a broad range of secondary patents, including any combination patents that may be relevant. It also requires checking the voluntary licensing policies of up to four different patent holders, and these policies are likely to vary in terms of which countries, which compounds, and which combinations are included and/or any other restrictions that maybe included that could affect procurement. Currently, there is no uniform,

publicly-accessible data source that combines this information in one easily accessible place.

The existence of licences, either voluntary or compulsory, has helped to overcome identified IP barriers in some instances. However, when two or three different patent-holders are involved, the situation becomes more complicated, as variations in licensing policies can mean that one component within an FDC may be accessed as a generic but not the other in a given country. The extent to which licensing helped to overcome IP barriers also varied by product and for many countries existing licences were insufficient to clear the legal path for the FDC, while for others, information was insufficient to make a determination.

A number of countries in which we had identified potential IP barriers to a particular FDC nevertheless had procured generic versions of such drugs. The extent to which this actually occurs is difficult to assess, as data on individual procurement transactions is not available from many countries (e.g. many middle income countries) and may depend on many issues including, for example, extent to which patent holders enforce their patents in different jurisdictions, level of risk aversion of different countries, procurement agencies or generic companies, strength of the granted/filed patents and use of various flexibilities by different countries (e.g. government use provisions).

In September 2011, the Global Fund Market Dynamics and Commodities (MDC) Ad Hoc Committee discussed the possibility of establishing incentives for greater utilisation of FDCs (e.g. by Global Fund grantees), which could potentially help spur the development of needed FDCs that are not currently on the market and enhance uptake of existing ones. However, due to the patenting of many antiretroviral (ARV) drugs in many LMICs, the ability of ARV manufacturers to make – as well as the ability of countries to procure – certain FDCs will likely be limited in some cases. More widespread public health-oriented licensing with improved and transparent terms and conditions would help to address this issue. The Medicines Patent Pool, a voluntary licensing mechanism with a mandate to negotiate licences from a public health perspective, is designed to facilitate the development and broader uptake of FDCs by making available the relevant intellectual property in a coordinated, transparent and predictable manner. This was a key rationale behind UNITAID's decision to support its establishment in 2010.

References

Avafia, T., Berger, J. and Hartzenberg, T. *The Ability of Select Sub-Saharan African Countries to Utilise TRIPS Flexibilities and Competition Law to Ensure a Sustainable Supply of Essential Medicines: A Study of Producing and Importing Countries*. TRALAC Working Paper No. 12, Stellenbosch 2006.

Boyd, W, "Dolutegravir—a promising antiretroviral in development" in *The Lancet*, Vol 12, 2012.

Correa, C. *Guidelines for the Examination of Pharmaceutical Patents: Developing a Public Health Perspective*. ICTSD, WHO, UNCTAD and UNDP, Geneva, 2007*a*.

Correa, C. *Intellectual Property and Competition Law: Exploring Some Issues of Relevance to Developing Countries*. ICTSD IPRs and Sustainable Development Programme Issue Paper No. 21, International Centre for Trade and Sustainable Development, Geneva, 2007*b*.

European Commission. *Executive Summary of the Pharmaceutical Sector Inquiry Report*. Brussels 2009.

Hemphill, S. and Sampat, B. *When do Generics Challenge Drug Patents?* Columbia Law and Economics Working Paper No. 379, 2011, available at: http://papers.ssrn.com/sol3/papers.cfm?abstract_id=1640512

Hindu Business Line, *Cipla unveils Triomune*, August 7, 2001, available at: http://hindu.com/businessline/2001/08/07/stories/020751zb.htm

Kapczynski, A. Harmonization and Its Discontents: A Case Study of TRIPS Implementation in India's Pharmaceutical Sector. *California Law Review*, 2009, 97:1571-1650.

Love, J. *Compulsory Licensing: Models For State Practice In Developing Countries, Access to Medicine and Compliance with the WTO TRIPS Accord*. Consumer Project on Technology, Washington, D.C. 2001.

Medicines Patent Pool, UNITAID, WHO, *Updated List Of Missing Drug Formulations For HIV Treatment*, 2011. Available at: http://www.who.int/selection_medicines/committees/expert/18/policy/policy4/en/index.html

MSF. *Untangling the web of antiretroviral price reductions*. 14th ed., Geneva 2011.

Nachega, J. et al. Treatment simplification in HIV-infected adults as a strategy to prevent toxicity, improve adherence, quality of life and decrease healthcare costs, *Patient Preference and Adherence*, 2011, 5:357-367.

't Hoen, E. *The Global Politics of Pharmaceutical Monopoly Power*. AMB, Diemen, the Netherlands, 2009.

Treatment Action Campaign. *TAC Complaint Increases Access to Efavirenz: MSD Finally Agrees to Grant Licenses on Reasonable Terms*. 2008, available at: www.tac.org.za/community/node/2329.

TWN. *Manual on Good Practices in Public-Health-Sensitive Policy Measures and Patent Laws*. Penang 2003.

UNAIDS/UNDP/WHO. *Using TRIPS flexibilities to improve access to HIV treatment.* Policy Brief, Geneva/New York, 2011.

UNDP. *Good Practice Guide: Improving Access to Treatment by Utilizing Public Health Flexibilities in the WTO TRIPS Agreement*. New York, 2010*a*.

UNDP, *Five Years into the Product Patent Regime: India's Response*. New York, 2010*b*.

Waning, B. et al. Intervening in global markets to improve access to HIV/AIDS treatment: an analysis of international policies and the dynamics of global antiretroviral medicines markets. *Globalization and Health*, 2010*a*, 6:9.

Waning, B. et al, A lifeline to treatment: the role of Indian generic manufacturers in supplying antiretroviral medicines to developing countries. *Journal of the International AIDS Society*, 2010*b*, 13:35.

WHO, *Antiretroviral Therapy for HIV Infection in Adults and Adolescents: Recommendations for a public health approach.* Geneva 2010.

WHO, *Essential Medicines: WHO Model List*, 2002

WHO, *Scaling up Antiretroviral Therapy in Resource-Limited Settings*, 2002b.

World Trade Organization, *Compulsory licensing of pharmaceuticals and TRIPS*. Geneva, available at: http://www.wto.org/english/tratop_e/trips_e/public_health_faq_e.htm

medicines
patent
pool

www.medicinespatentpool.org